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Diverse physiological consequences of long-term sucrose consumption in female rats

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Abstract
Although a considerable amount of work has addressed the short-term consequences of sucrose ingestion on a variety of morphological, physiological and hematological measures, relatively few studies have investigated these parameters following long-term sucrose intake. Results of the present experiments indicated that female rats given *ad libitum* access to a 10% sucrose solution for 9 months were conspicuously larger and had significantly heavier thyroid and spleen weights compared to rats offered either a restricted (20 min) daily sucrose option or control rats given only water. Rats given free access to sucrose also displayed abnormal serum levels of creatinine, sodium, phosphorus, alkaline phosphatase, alanine aminotransferase, uric acid and cholesterol which could indicate dysfunction in many organs including the kidney and liver. In the brain, however, chronic sucrose access was not associated with any discernable changes in neuronal or glial cell density within selected brain regions, but brain weight was found to be highly negatively correlated ($r = -0.97$) with total sucrose intake. Finally, we report that high doses of estradiol can significantly attenuate the intake of sucrose in female rats. Together these findings demonstrate that free access to a sucrose solution for long periods can induce profound effects on rat physiology and may have important implications for the management of diet in humans.

Keywords: *Sucrose, physiology, female, rat*

Introduction

There is concern over the increasing consumption of refined carbohydrates particularly of sucrose (sugar) by humans (Anderson 1982). Evidence suggests that the excessive intake of sucrose can lead to obesity (Ramirez 1987), increase the risk for diabetes (Lazar 2005) and hypertension in humans (Ahrens 1974). In animal studies, rats given the option to consume a sucrose–water solution will ingest approximately 50–60% of their daily caloric value from sucrose and exceed the total daily caloric intake of control subjects by 20% (Kanarek and Marks-Kaufman 1979, 1988). The persistent intake of sucrose is known to elevate blood triglycerides and insulin levels leading to over-eating and excessive weight gain in rats (Kanarek and Hirsch 1977; Faust et al. 1978; Toida et al. 1996; El Hafidi et al. 2001; Kanazawa et al. 2003). There is also evidence that rats experience addiction, withdrawal and relapse to sugar added to the diet (Wideman et al. 2005). The robust proclivity for sucrose consumption may reflect the fact that it interacts with the endogenous dopaminergic (Hajnal and Norgren 2002, 2005) and opioidergic (Blass and Shah 1995; Cichelli and Lewis 2002) signaling pathways within the brain (Brennan et al. 2001; Avena et al. 2005), and why its addictive properties have been compared to nicotine and morphine (Colantuoni et al. 2002).

Considerable work has demonstrated that diets high in sucrose can have significant negative effects on the morphological and histological characteristics of the liver (Vrana and Fabry 1983; Poulsom 1986), kidney (Durand et al. 1968; Bender and Thadani 1970) and retina (Yanko et al. 1972). The breadth of this

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pathology has lead some investigators to propose that diets high in sucrose may cause enhanced oxyradical production and reduced antioxidant defense (Busserolles et al. 2002). Interestingly, although the brain is particularly sensitive to oxidative stress (Butler and Bahr 2006), and may show significant changes in neuronal excitability after sucrose ingestion (Galic and Persinger 2005), little investigation has been made into whether the brain shows any histological changes in response to prolonged sucrose intake.

Some evidence has proposed that female rats display a disproportionately greater affinity to palatable carbohydrates (glucose, sucrose and fructose) and may suffer greater morbidity when given the option to consume them *ad libitum* compared to male cohorts (Valenstein et al. 1967; al Nagdy et al. 1970; Hirsch et al. 1982; Sclafani et al. 1987; Kanarek and Homoleski 2000; Eckel and Moore 2004). Precisely why females respond differently than males is not known, however, these discrepancies might arise from hormonal differences between the sexes. There is also strong evidence suggesting that cycling of gonadal hormones, particularly of estrogen, in humans and rats might underlie changing gustatory preferences for sweet compounds (Than et al. 1994; Galic and Persinger 2002). Moreover, ovariectomy has been demonstrated to significantly increase food intake and weight gain in female rats (Kanarek and Beck 1980), which can be reversed through periodic estradiol application (Geary and Asarian 1999; Asarian and Geary 2002). Currently the outcome of estradiol administration on the pattern of sucrose consumption in intact female rats is not known. The present set of experiments were performed to systemically evaluate the consequences of long-term sucrose intake on multiple measures of blood serum, organ weight and cell densities within select brain regions and furthermore describe the consequences of estradiol treatment on sucrose intake in rats.

Materials and methods

Experiment I: Long-term sucrose consumption

To examine the effects of long-term sucrose consumption on an array of physiological indices, thirteen young adult female Wistar rats served as subjects. They were housed individually under standard laboratory conditions and provided free access to lab chow (Harlan Teklad, 8640) and water. All procedures were approved by the local Animal Care Committee and were in compliance with the Canadian Council on Animal Care guidelines. Sample sizes were chosen to generate suitable statistical power for the expected effect size and duration of the study.

Rats were randomly assigned to each of the three treatment conditions. Five rats were given restricted access to a 10% sucrose solution for 20 min a day while a second group of four rats were provided *ad libitum* access to a 10% sucrose solution for 24 h a day. A third group of animals ($n = 4$) were designated as controls and offered only tap water to drink. Rats in the restricted access group received a 10% sucrose solution at about the same time each day (17:00 h local time) for 20 min for 9 successive months. Once weekly this group of rats were permitted all-day access to the sucrose solution to maintain the "reinforcement" of the compound. After each session, the volume of sucrose–water and tap water consumed was recorded to the nearest ml and refreshed. The second group of animals were permitted *ad libitum* access to the 10% sucrose solution for 24 h a day for 9 successive months. Each day the volumes of sucrose–water and tap water were measured and recorded to the nearest ml and refreshed.

Upon completion of the study, all subjects were sacrificed for measurement of body weight along with wet weights of the thyroid, thymus, spleen, pancreas, adrenals, ovaries, kidneys, brain and pituitary. Trunk blood from the control and *ad libitum* sucrose groups were also collected for later analysis of serum for aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), glucose (GLU), blood urea nitrogen (BUN), creatinine (CRE), sodium chloride (NA), potassium (K), chloride (CL), calcium (CA), phosphorus (PHOS), uric acid (UA), albumin (ALB), triglycerides (TRIG) and cholesterol (CHOL).

The brains from the control and *ad libitum* sucrose groups were later fixed in a solution of ethanol, formalin and acetic acid and embedded in paraffin wax blocks for sectioning on a microtome. Ten micrometer sections from the anterior to posterior commisure were stained with toluidine blue O (Persinger 1977). Under light microscopy, neurons and glial cells were counted within a 6 × 6 grid (area $= 0.093\,mm^2$) using a 1000 × oil immersion lens. Distinction between neuron and glial cells were based upon cellular size and cytoplasmic distribution of Nissl staining (Ling et al. 1973). A total of six samples from the ventromedial hypothalamus (VMH), nucleus accumbens (Acb), lateral hypothalamus (LH), ventral tegmental area (VTA), arcuate nucleus of the hypothalamus (Arc), ventral endopiriform nucleus (VEn), periventricular hypothalamus (Pe), lateral septal [intermediate] nucleus (LSI), CA3 hippocampus (CA3), and the ventral lateral thalamus (VL) as defined by (Paxinos and Watson 1998) were quantified for each subject. All cell counts are presented as the number of cells/mm^2. The former five structures were selected for their putative involvement in consummatory behaviors (Yamamoto 2003), while the latter five areas served as a comparator group within the treatment condition.

Experiment II: Estradiol administration and sucrose ingestion

To examine whether peripheral estrogen administration influenced the ingestion pattern of a 10% sucrose solution, twenty young adult female rats were used. In three separate blocks of experiments, rats were presented with a 10% sucrose solution option for about 45 days. After 2 weeks of baseline consumption, each rat was injected subcutaneously with either: 0.1, 0.5, or 1.0 mg/kg of β-estradiol 3-benzoate (low, medium and high doses, respectively) or the vehicle (sesame seed oil) every 4 days until eight injections were delivered. It has been hypothesized that hormonal injections at a frequency that mimics the endogenous reproductive rhythmicity of the animal may yield the most physiologically meaningful effects (Morrison et al. 2006). The daily volumes of sugar–water and tap water consumed were recorded to the nearest ml and refreshed. Twenty-four hours after the last injection, rats were sacrificed for measurements of body weight along with wet weights of the thyroid, thymus, spleen, pancreas, adrenals, ovaries, kidneys, brain and pituitary.

Results

Experiment I: Long-term sucrose consumption

Rats maintained on the sucrose restricted option drank on average (standard error of the mean in parenthesis) about 14.1 (0.9) ml of sucrose–water and 32.9 (2.3) ml of tap water per day. Those rats in the *ad libitum* sucrose group consumed on average about 117.5 (11.3) ml of sucrose–water and 3.5 (0.5) ml of tap water per day. In this group, the initial volume of sucrose consumed per month began around 60 ml per day but steadily increased over 3 months then asymptoted. The means and standard error of the means for each of the 9 months of sucrose intake for both the *ad libitum* and restricted sucrose groups appear in Figure 1.

The results of the body weight and organ weight measurements that displayed statistical significance appear in Figure 2. A one-way analysis of variance (ANOVA) determined a significant difference in body weight [$F(2,12) = 89.01$, $p < 0.001$], thyroid weight [$F(2,12) = 8.12$, $p < 0.01$] and spleen weight [$F(2,12) = 11.16$, $p < 0.001$] between the treatment conditions. *Post hoc* analysis (Tukey) indicted that the source of this effect was primarily due to the larger body and organ weights of the animals maintained on the *ad libitum* sucrose option compared to the both the sucrose restricted and control groups, which did not differ significantly from one another. Data on organ weights lacking statistical significance are not shown. Although the brain weights between the *ad libitum* sucrose group and controls did not differ, correlational analysis (using Spearman ρ and Pearson r) of the brain weight as a function of total sucrose intake in the *ad libitum* group revealed a strong ($\rho = -0.99, r = -0.97$) and statistically significant ($p < 0.05$) inverse correlation such that the higher total sucrose intake of a given rat, the lower the observed wet brain weight. This relationship was not seen between total water intake and brain weight in this group.

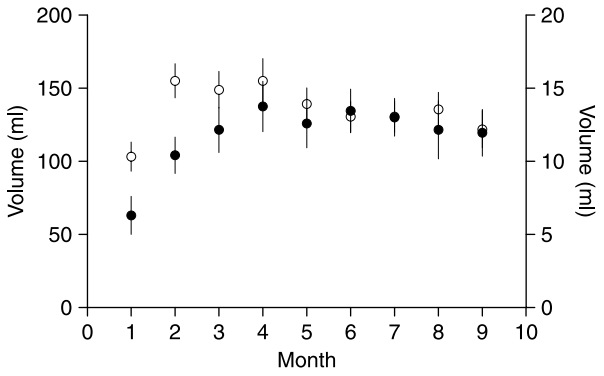

Figure 1. Mean volumes of 10% sucrose consumed (in ml) by female rats in the *ad libitum* (filled circles, left axis) and restricted access (open circles, right axis) sucrose groups over 9 months. Error bars represent standard error of the mean.

The means and standard deviations for the values of the blood chemistry analysis that showed significant differences appear in Table I. A one-way ANOVA discerned significant differences in CRE [$F(1,7) = 25.46$, $p < 0.01$], NA [$F(1,7) = 6.59$, $p < 0.05$], PHOS [$F(1,7) = 8.75$, $p < 0.05$], ALP [$F(1,7) = 37.12$, $p < 0.01$], ALT [$F(1,7) = 7.87$, $p < 0.05$], UA [$F(1,7) = 65.93$, $p < 0.001$] and CHOL [$F(1,7) = 14.12$, $p < 0.01$] between the *ad libitum* sucrose and control groups. With the exception of CRE and CHOL, sucrose animals showed significantly lower mean serum values than controls. Serum measures of BUN ($p = 0.057$) and TRIG ($p = 0.087$) were also strongly influenced by the sucrose treatment, decreased and increased values, respectively. All remaining blood chemistry variables were not statistically different between the groups.

Table II displays the means and standard deviations for the numbers of neurons and glial cells for the structures investigated. The results of a one-way ANOVA indicated that neither the number of glial cells or neurons within the any of the 10 structures from the brains of rats in the *ad libitum* sucrose group differed significantly (all $p > 0.05$) from controls.

Experiment II: Estradiol administration and sucrose ingestion

The mean volume of sucrose consumed during baseline by each of the 4 treatment groups did not differ significantly ($p > 0.05$) from one another. The ratio of sucrose consumed before and after each injection was computed for each treatment condition

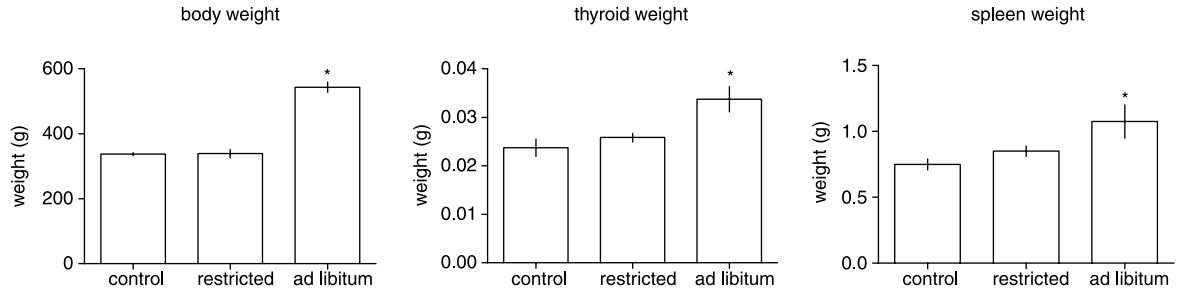

Figure 2. Mean body weight and select organs weights (in grams) of rats maintained on an *ad libitum* sucrose option, a restricted sucrose option or control rats given only water. Significantly heavier body weights and thyroid and spleen weights were observed in rats offered the *ad libitum* sucrose solution. Error bars represent standard error of the mean. An asterisk denotes groups that differ significantly ($p < 0.05$) from controls.

Table I. The means and standard deviations (in parenthesis) for blood serum values of rats from the control and *ad libitum* sucrose group.

	CRE	NA	PHOS	ALP	ALT	UA	CHOL
Control	20.7 (5.5)	149.7 (1.5)	3.02 (0.15)	186.2 (46.6)	67.5 (11.4)	103.0 (8.7)	1.85 (0.20)
Sucrose	44.0 (7.3)	144.7 (3.5)	2.46 (0.35)	36.7 (15.1)	45.5 (10.7)	52.2 (8.9)	2.93 (0.53)

Only measures that showed significant ($p < 0.05$) differences are presented. The units for the blood measures are: CRE (mg/dl), NA (mEq/l), PHOS (mg/dl), ALP (U/l), ALT (U/l), UA (mg/dl) and CHOL (mmol/l).

(low, medium and high estradiol or vehicle) and averaged over eight sessions. For example, a ratio of 0.90 indicated that a rat consumed 90% of the volume of sucrose during the 24 h following the treatment injection compared to the 24 h period before the treatment. Mean ratios of sucrose ingestion for the 4 treatment conditions are presented in Figure 3.

Analysis of variance determined a significant difference between treatment condition [$F(3,19) = 13.1$, $p < 0.05$] and the mean ratio of sucrose consumed. *Post hoc* analysis (Tukey) indicated that both the medium and high estradiol-treated rats drank significantly less sucrose following each injection than did rats receiving the low dose of estradiol or the vehicle. The sucrose consumption ratios of the medium and high dose estradiol did not differ significantly from one another, nor did the low dose estradiol and vehicle groups differ significantly from one another.

Results of the morphometric and organometric measurements that were statistically significant appear in Figure 4. Analysis of variance revealed a significant difference for mean body weight [$F(3,19) = 3.40$, $p < 0.05$], thymus weight [$F(3,19) = 4.97$, $p < 0.05$] and pituitary weight [$F(3,19) = 3.80$, $p < 0.05$] between the groups. *Post hoc* analysis (Tukey) revealed that all differences were between rats who received the high dose estradiol compared to controls. Rats in the high estradiol treatment group exhibited significantly smaller body and thymus weights, but showed appreciably larger pituitary weights than subjects in the reference condition. Data on organ weights lacking statistical significance are not shown.

Table II. The means (M) and standard deviations (SD) for the numbers of neurons and glial cells (counts adjusted to mm^2) for 10 brain regions from rats permitted free access to a sucrose solution or controls.

	Control				Sucrose			
	Neuron		Glia		Neuron		Glia	
	M	SD	M	SD	M	SD	M	SD
VMH	1666.7	189.2	1182.8	178.5	1881.7	464.5	1473.1	301.1
Acb	1361.3	198.9	1379.6	124.7	1612.9	507.5	1330.1	152.7
LH	1038.7	345.2	1344.1	60.2	788.2	155.9	1330.1	139.8
VTA	837.6	151.6	1200.0	302.2	908.6	153.8	1338.7	143.0
Arc	1365.6	309.7	1226.9	458.1	1557.0	389.2	1371.0	116.1
VEn	1226.9	405.4	1038.7	125.8	1441.9	364.5	1096.8	131.2
Pe	1057.0	240.9	1545.2	604.3	1290.3	122.6	1468.8	366.7
LSI	1222.6	132.3	1016.1	210.8	1258.1	140.9	1245.2	107.5
CA3	1983.9	108.6	1133.3	292.5	2329.0	504.3	1415.1	479.6
VL	958.1	180.6	1164.5	132.3	918.3	341.9	1371.0	221.5

There were no significant differences between the groups for any of the brain structures measured.

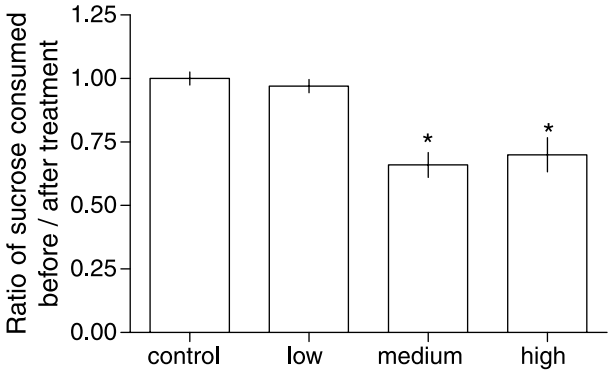

Figure 3. Mean ratio of sucrose consumed following administration of either low (0.1 mg/kg), medium (0.5 mg/kg) or high dose estradiol (1.0 mg/kg) or the vehicle (control). Groups that received the medium and high estradiol treatment consumed significantly less sucrose during the 24 h period following injection compared to animals receiving the low dose estradiol or the vehicle. Error bars represent standard error of the mean. An asterisk denotes groups that differ significantly ($p < 0.05$) from controls.

Discussion

The present set of experiments have shown that prolonged sucrose intake can cause marked perturbations in the homeostasis of several morphological, physiological and hematological parameters in the rat. The most robust impact of sucrose consumption was found on body weight. In comparison to the sucrose restricted and control groups, rats offered *ad libitum* access to the sucrose solution were about 60% heavier at the end of 9 months of observation. This finding is consistent with extensive literature showing marked weight gain and increased adiposity in rats following periods of extended sucrose intake (Kanarek and Hirsch 1977; Kanarek and Marks-Kaufman 1979; Hirsch et al. 1982). Interestingly, rats given restricted access to the sucrose solution for 20 min a day were morphometrically identical to controls who received only water. Previously, Hirsch and Walsh (1982) reported a similar finding showing that rats offered a sucrose solution only during the photophase (12 h) did not increase their caloric intake or weight gain relative to a reference group. Together these results suggest that a restricted sucrose regime (from 20 min up to 12 h a day) may function experimentally as a practical "negative control" that could be included in future studies to account for non-specific effects of sucrose intake.

We also noted marked changes to thyroid and spleen morphology in rats who received the *ad libitum* sucrose option. Of particular interest was the increased weight of the thyroid gland in this population. Since there is evidence for altered synthesis of arachadonic-derived prostaglandins (El Hafidi et al. 2001) and enlargement of the spleen (this study, but also see Busserolles et al. (2003)) following sucrose-enhanced diets, we interpreted the enlarged thyroid to reflect an inflammatory thyroiditis-like condition. Therefore, thyroid gland dysfunction would predict impaired metabolic rate and efficiency as previously suspected (Busserolles et al. 2002; Levine et al. 2003), and be consistent with difficulty in body weight regulation.

A prominent disruption to blood chemistry was also evident in rats given the *ad libitum* sucrose option. Sodium and PHOS were the most strongly affected of the electrolytes, both showing low serum concentrations. Deficiencies in electrolytes can be the result of changes in blood volume due to increased total fluid intake (dilution), as we have observed here, or can be related to impaired excretion due to kidney dysfunction (for review see Verbalis (2003)). Rosenmann et al. (1971) have reported that rats fed a high sucrose diet developed diffuse glomerulosclerosis that mimicked both experimental and clinical diabetic nephropathy. The existence of such a nephropathy in our population would also explain the abnormal serum concentrations of CRE and BUN (waste products of metabolism) and collectively suggest that prolonged sucrose intake may negatively impact on renal physiology and function.

We also noted deficiency in blood enzyme concentrations, specifically to ALT and ALP. These liver enzymes are normally a marker for hepatic disease when elevated (Limdi and Hyde 2003), however, low levels may suggest nutritional inadequacies. It is known that protein deficiency, but not calorie deficiency, is sufficient to produce a reduction in

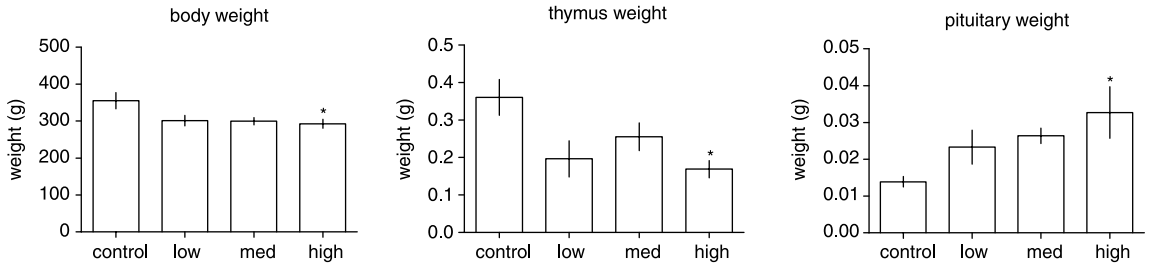

Figure 4. Mean body weight and select organ weights (in grams) of rats treated with either low (0.1 mg/kg), medium (0.5 mg/kg) or high dose estradiol (1.0 mg/kg) or the vehicle (control). A significantly lower body weight and thymus weight, but heavier pituitary weight was recorded in rats treated with the high dose estradiol compared to controls. Error bars represent standard error of the mean. An asterisk denotes groups that differ significantly ($p < 0.05$) from controls.

serum levels of liver enzymes (Waterlow 1970), and interestingly these two features have been observed in rats maintained on sucrose-enhanced diets (Collier and Bolles 1968). In addition, we report significant increases in serum CHOL, and to a lesser extent, TRIG. Predictably these measures would be elevated in animals that exceed their optimal caloric intake, and represent a well established characteristic of sucrose-supplemented diets (Cohen 1972; Waddell and Fallon 1973; Kanazawa et al. 2003). Therefore the general impression of these blood serum results suggests the existence of possible polyorgan dysfunction in conjunction with poor long-term macronutrient selection that should be discussed in the context of a general metabolic syndrome.

We also explored the hypothesis that long-term sucrose intake could produce an effect on cellular density within selected brain regions that modulate ingestive behaviours. This was based on evidence that rats fed a high sucrose diet showed significant reductions in brain-derived neurotrophic factor (Molteni et al. 2002) which is considered essential for neuronal growth, differentiation and survival (Leibrock et al. 1989). However our data indicated that female rats who consumed sucrose for protracted periods did not show any apparent anomalies in the density of neuronal or glial cell populations within selected limbic and diencephalic regions compared to controls. We did, however, discern a prominent inverse correlation between total sucrose consumed and brain weight ($\rho = -0.99$, $r = -0.97$). Therefore the more sucrose consumed by rats, the lower the brain weight. This finding, along with the blood serum results showing hyponatremia (low sodium) in the *ad libitum* sucrose group may reflect a hypo-osmolar state in the brain (Riggs 2002). Because hyponatremia can be induced by excessive fluid consumption (Hariprasad et al. 1980), that preferentially affects the brain (Sterns and Silver 2006), a reduction in extracellular space could evolve over time (Andrew 1991), and may explain how brain weight was inversely correlated with sucrose intake.

Finally, we determined the effects of periodic estradiol administration on sucrose intake. Our results indicated that female rats treated with the medium and high doses of estradiol exhibited robust reductions in sucrose consumption during the 24 h after injection. In comparison, rats treated with either the low dose estradiol or the vehicle showed little change in sucrose intake following injection. Prior work has shown that estradiol injection into ovariectomized rats can reduce meal volume within minutes following administration (Geary et al. 1995) and can last for 1–2 days (Tarttelin and Gorski 1973). Similarly in our study, the treatment with estradiol appeared to produce a transient reduction in sucrose intake which returned to near baseline within 48 h post-injection. We conclude that administration of high concentrations of estradiol is sufficient to suppress sucrose intake despite its high palatability and reinforcing properties, and moreover that sucrose ingestion is equally vulnerable to the same mechanisms of gastric suppression following estradiol treatment as other foodstuffs (Wade 1972).

In addition to changes in ingestive behaviours, rats who received the high dose of estradiol also showed differences in organ and body weight measurements. These rats exhibited lighter body and thymus weights, but heavier pituitary weights compared to the control group. Although we did not measure total food consumption, the body weight reduction may be the result of a decrease in chow intake. It may be relevant to note that significant suppression of sucrose intake could be achieved following treatment with the medium dose of estradiol but without significant changes in body and organ weights in those rats.

In summary, the present experiments have shown that *ad libitum* long-term sucrose intake can have a negative influence on a variety of morphological, physiological and hematological parameters in the adult female rat. The most profound effect of sucrose consumption was on body weight which has been previously described to closely resemble that of a clinically obese population (Kanarek and Hirsch 1977). If obesity in adult humans is associated with elevated mortality and greater risk for coronary heart disease, hypertension, hyperlipidemia, diabetes, gallbladder disease, osteoarthritis and certain forms of cancer (Ogden et al. 2003), then the role of sucrose in the generation of obesity should be seriously considered when counselling patients on dietary selection.

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